Original Article

Identification of *GINS1* as a potential prognostic biomarker for sarcoma using bioinformatic analysis

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Background: The GINS complex is related to cancer development, invasion, and poor prognosis in multiple tumors. In the study, we attempted to investigate the prognostic value of *GINS1* in sarcoma patients.

Methods: We analyzed *GINS1* expression using Tumor IMmune Estimation Resource (TIMER) 2.0, Gene Expression Omnibus (GEO; GSE21122, GSE39262, and GSE21050), and The Cancer Genome Atlas (TCGA) databases. The prognostic value of *GINS1* was explored using the survival and survminer packages of R. Genetic alteration analysis was investigated using cBioPortal. The Cell-type Identification by Estimating Relative Subsets of RNA Transcripts (CIBERSORT) R script was used for the immunocyte infiltration analysis. MicroRNAs (miRNAs) targeting *GINS1* were predicted using GEO (GSE69470) and MicroRNA Target Prediction Database (miRDB).

Results: We found that *GINS1* was overexpressed in sarcoma, especially in metastatic samples, and was associated with a worse prognosis. High *GINS1* expression was a poor prognostic indicator for sarcoma patients. Moreover, *GINS1* alteration was associated with worse survival of sarcoma patients. Immune infiltration analysis indicated that *GINS1* expression was correlated with the infiltration of M0 and M2 macrophages in sarcoma. Finally, the miRNA hsa-miR-376a-3p was identified to potentially regulate *GINS1* in sarcoma.

Conclusions: These results indicate that *GINS1* may be a promising prognostic biomarker and therapeutic target for sarcoma.

Keywords: Bioinformatic analysis; prognostic biomarker; sarcoma; *GINS1*

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Introduction

Sarcomas, encompassing soft-tissue sarcomas (STS) and bone sarcomas, are a heterogeneous group of malignancies arising from mesenchymal tissues (1). They are rare tumors that comprise approximately 1% of adult malignancies, and nearly 15% of pediatric malignancies (2,3). The current World Health Organization classification contains more than 100 histological subtypes of sarcomas (4,5).

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This diversity results in the complexities of personalized therapies (5,6). The most frequent subtypes of STS include liposarcomas, leiomyosarcomas, and undifferentiated pleomorphic sarcomas (5). Frequent primary bone sarcoma subtypes include osteosarcoma, Ewing's sarcoma, and chondrosarcoma (7). The 5-year survival rate for patients with sarcoma is approximately 60–70%, however, it drops to only 16% for patients with distant metastasis (8,9). Various sarcoma treatments include local surgery, chemotherapy, and radiotherapy, more commonly neoadjuvant chemotherapy and preoperative radiotherapy (9-11). Nevertheless, the life expectancy of sarcoma patients with metastasis remains dismal. Although progress in targeted therapy has significantly improved the prognosis of several cancers, advances with targeted therapy for sarcomas are very few (10). Hence, molecular mechanisms and potential biomarkers of sarcomas are urgently required to improve their treatment.

The GINS complex is the initial of the Japanese numerals 5-1-2-3 (go-ichi-ni-san) and comprises the *SLD5*, *PSF1*, *PSF2*, and *PSF3*, encoded by *GINS4*, *GINS1*, *GINS2*, and *GINS3* genes. The GINS complex serves as a replicative helicase during DNA replication along with CDC45 and MCM2-7 (12). Previous studies have shown that the overexpression of *GINS1* is related to cancer development, invasion, and worse survival of multiple tumor types, such as glioma, lung cancer, and hepatocellular carcinoma (13-15). Besides, *GINS1* has been identified to be a poor prognostic factor in synovial sarcoma (16).

However, according to our knowledge, there is a lack of specialized study on the prognostic impact of *GINS1* on all sarcoma types. For the first time, we attempted to explore the role of *GINS1* in the progression and poor prognosis of sarcomas by bioinformatic analysis, which has been widely used in the study of malignant tumors (17). We established that sarcomas associated with metastasis and poor prognosis expressed high levels of *GINS1*. We also observed that *GINS1* alteration was significantly related to a worse prognosis in sarcoma, indicating the critical role of *GINS1* in sarcoma. These results suggest that GINS1 could serve as a potential prognostic biomarker for sarcoma. We present the following article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-524/rc).

Highlight box

Key findings

- *GINS1* may be a promising prognostic biomarker and therapeutic target for sarcoma.

What is known and what is new?

- The GINS complex is related to cancer development, invasion, and poor prognosis in multiple tumors.
- We attempted to explore the role of *GINS1* on the progression and poor prognosis of sarcomas.

What is the implication, and what should change now?

- *GINS1* may be used as a therapeutic targeted biomarker for patients with sarcoma in the future.

Methods

Expression level analysis of GINS1 in sarcoma

The Tumor IMmune Estimation Resource 2.0 (TIMER 2.0; http://timer.cistrome.org) (18) database was used to investigate the transcription level of *GINS1* in different types of tumors and the corresponding sarcoma samples. Two expression profiling datasets (GSE21122, GSE39262) were queried from the NCBI Gene Expression Omnibus (GEO; https://www.ncbi.nlm.nih.gov/geo/) database (19). The messenger RNA (mRNA) profiles of GSE21122 containing 149 sarcoma and 9 normal fat tissues and GSE39262 containing 46 sarcoma cell lines and 5 untransformed primary cells were detected by Affymetrix Human Genome U133A Array (Affymetrix, Santa Clara, CA, USA). Differential expression of *GINS1* between the sarcoma and control groups in the 2 datasets were analyzed using Wilcoxon rank-sum test. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Expression level analysis of GINS1 in metastatic sarcoma

A total of 174 sarcoma patients with complete metastasis information were obtained from The Cancer Genome Atlas (TCGA; https://cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga) (20) database. GSE21050, which contained 121 metastatic sarcoma samples and 188 non-metastatic samples, was acquired from the GEO database. Differential expression of *GINS1*

Table 1 Clinicopathological characteristics of sarcoma patients from TCGA database

Characteristics	Patients (N=256)	
	No.	%
Sex		
Female	139	54.30
Male	117	45.70
Age		
≥60 years old	140	54.69
<60 years old	116	45.31
Race		
Asian	5	1.95
Black or African American	18	7.03
Caucasian	224	87.50
Unknown	9	3.52
Metastasis at diagnosis		
Metastatic	56	21.88
Non-metastatic	118	46.09
Unknown	82	32.03
Vital status		
Alive	158	61.72
Dead	98	38.28

TCGA, The Cancer Genome Atlas.

between the metastatic and non-metastatic sarcomas were analyzed using Wilcoxon rank-sum test, respectively, in these 2 datasets.

Survival analysis

To investigate the effect of *GINS1* on sarcoma prognosis, 256 sarcoma patients in TCGA were divided into high and low *GINS1* expression groups according to the median; the patient information is displayed in *Table 1*. Overall survival (OS) and multivariate Cox regression analyses of sarcoma patients were performed by the survival and survminer packages in R.

Genetic alteration analysis

cBioPortal (http://www.cbioportal.org/) (21) is a user-friendly database providing large-scale genomic datasets for various tumors online. TCGA Sarcoma project (TCGA PanCancer Atlas), involving data from 255 sarcoma specimens, was utilized for further genetic alteration and survival analysis of *GINS1*. The OncoPrint module was used to acquire the alteration frequency and mutation type of *GINS1* in sarcoma samples. The impact of *GINS1* mutation on sarcoma prognosis was obtained via the survival module.

Immune infiltration analysis

The relative infiltration ratios of 22 types of immunocytes in 256 sarcoma samples were estimated by the Cell-type Identification by Estimating Relative Subsets of RNA Transcripts (CIBERSORT) R script. Correlation between differentially expressed *GINS1* and immunocyte infiltration were explored using the corr.test function of R. Differential infiltration of immunocytes between high-*GINS1* expression and low-*GINS1* expression samples were analyzed using Wilcoxon rank-sum test.

The miRNA-GINS1 mechanism prediction

The GSE69470 dataset, which contains 68 sarcoma cell lines and 5 normal counterpart cells, was retrieved from the GEO database. The miRNA expression was measured with NanoString nCounter Human miRNA Expression Assay (https://nanostring.com/). The differentially expressed miRNAs (DEMs) analysis was carried out using GEO2R provided by the GEO database with the DEM screening criteria set as |log fold change (FC)| >1.5 and P<0.05. All the DEMs were visualized using the ggplot2 and pheatmap packages of R (22,23). We used MicroRNA Target Prediction Database (miRDB; http://mirdb.org/), an open-source platform for miRNA target prediction, to acquire miRNAs likely to target *GINS1*. A Venn diagram was constructed using the ggvenn package of R.

Statistical analysis

Differences between sample groups were compared using Wilcoxon rank-sum test. Survival difference was tested by the log-rank method. Correlation analysis was performed using the Spearman method. A P value <0.05 represented a significant difference. All statistical analyses were carried out using R version 4.2.1.

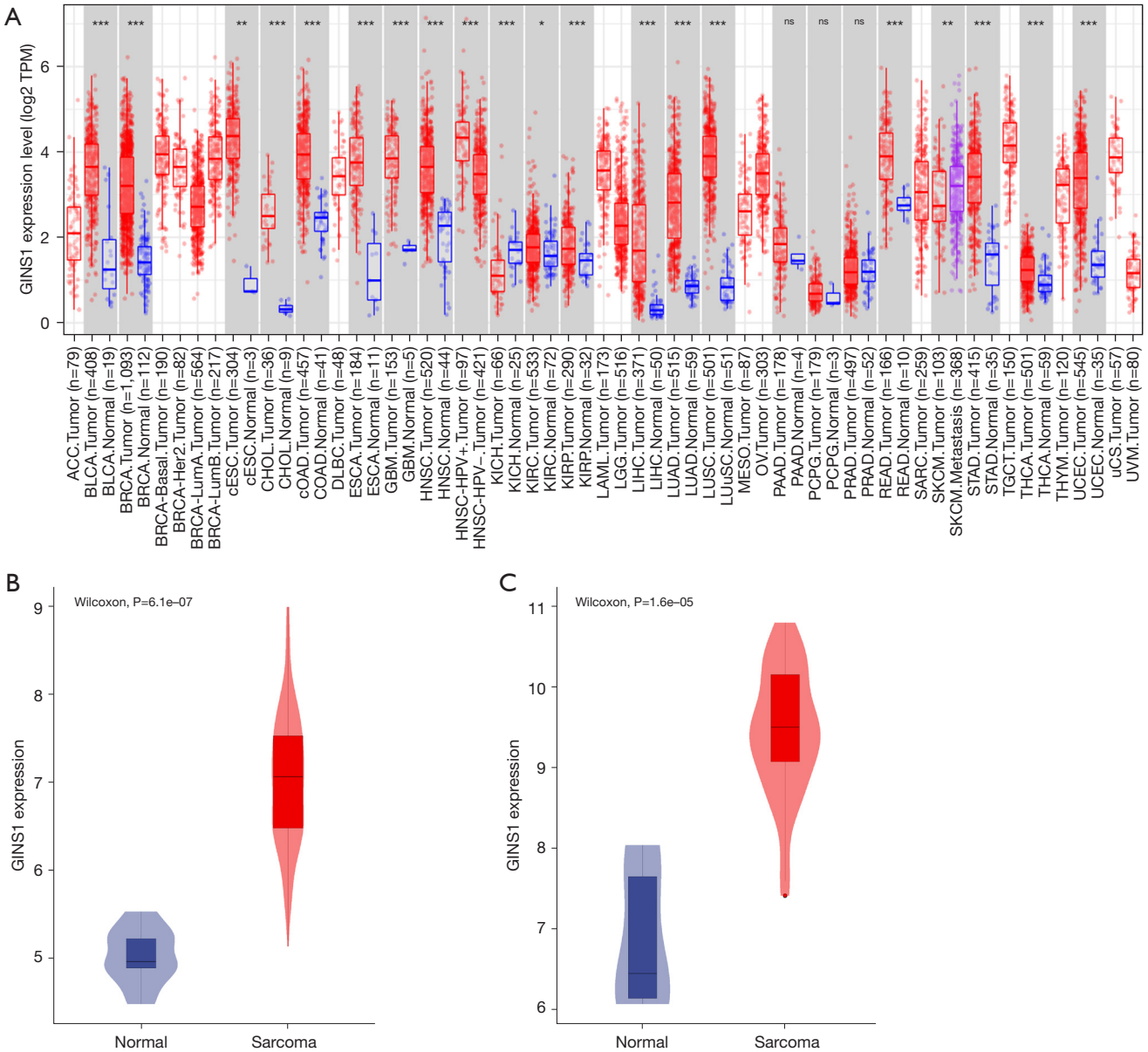

Figure 1 The expression level of *GINS1* in sarcoma. (A) Pan-cancer expression level of *GINS1* in TIMER 2.0 database. (B) *GINS1* expression in soft-tissue sarcoma and normal fat tissues (GSE21122). (C) *GINS1* expression in sarcoma cell lines and untransformed primary cells (GSE39262). *, P<0.05; **, P<0.01; ***, P<0.001; ns, no significant; TPM, transcripts per million.

Results

GINS1 expression in sarcoma

Using the TIMER 2.0 database, we found that the mRNA expression of *GINS1* was upregulated in various tumors (*Figure 1A*). Subsequently, in the GSE21122 dataset, significantly higher *GINS1* expression was observed in STS than in fat tissues (P=6.1e-07, *Figure 1B*). Similarly, in the GSE39262 dataset, *GINS1* expression was remarkably higher in sarcoma cell lines than in the control cells (P=1.6e-05, *Figure 1C*). These findings reveal that *GINS1* is overexpressed in sarcoma, similar to other tumors.

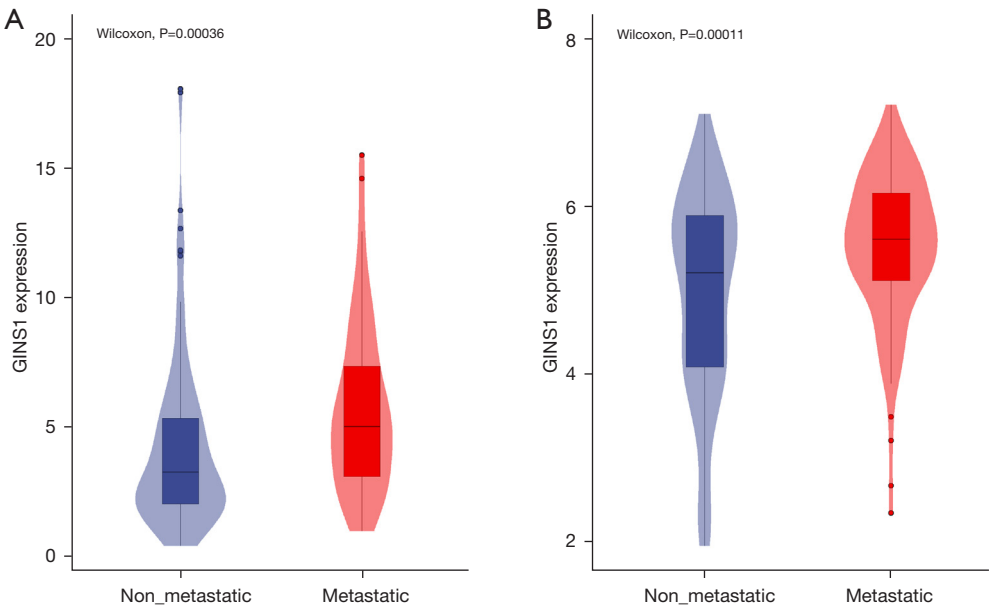

Figure 2 GINS1 expression in metastatic and non-metastatic sarcoma samples. (A) *GINS1* expression in TCGA database. (B) *GINS1* expression in GSE21050 dataset. TCGA, The Cancer Genome Atlas.

GINS1 expression in metastatic sarcoma

In TCGA database, significantly higher *GINS1* expression was observed in metastatic sarcomas than in non-metastatic samples (P=0.00036, *Figure 2A*). In the GSE21050 dataset, *GINS1* expression was remarkably higher in the metastatic sarcomas than in non-metastatic samples (P=0.00011, *Figure 2B*). The results indicate that *GINS1* may potentially promote the metastasis and progression of sarcoma.

The prognostic value of GINS1 in sarcoma

By performing survival analysis, we found that sarcoma patients with high *GINS1* levels predicted shorter OS compared to those with low *GINS1* levels (P=0.005, *Figure 3A*), indicating that highly expressed *GINS1* portended a worse prognosis in sarcoma.

A multivariate Cox regression analysis, including *GINS1* level (high *vs.* low), sex, age, and race, was conducted to determine whether *GINS1* is an independent prognostic indicator for sarcomas. Compared with low *GINS1* expression, sarcoma patients with high *GINS1* expression had a higher risk of death [hazard ratio (HR) = 1.80, 95% confidence interval (CI): 1.185–2.7, P=0.006, *Figure 3B*], indicating that high *GINS1* expression was a poor prognostic indicator for sarcomas.

Analysis of genetic alteration of GINS1 in sarcoma

In the cBioPortal database, genetic alteration of *GINS1* was detected in 8% of the probed sarcoma patients using the OncoPrint visual summary (*Figure 4A*). Using the Kaplan–Meier plot, patients with *GINS1* alteration displayed worse OS and disease-free survival (DFS) than those in the unaltered group (P<0.05, *Figure 4B,4C*). Hence, *GINS1* may play an important role in sarcoma progression and prognosis.

Analysis of GINS1-related immunocyte infiltration in sarcoma

To validate the effect of *GINS1* on immunocyte infiltration in sarcoma, we revealed the immune infiltration differences of 22 varies of immunocytes between high and low *GINS1* expression sarcomas via CIBERSORT method. The immunocyte infiltration ratios in various sarcoma patients were different (*Figure 5A*). We explored the correlation between differentially expressed *GINS1* and immunocyte infiltration in sarcomas and found that *GINS1* expression was positively associated with M0 macrophages, resting

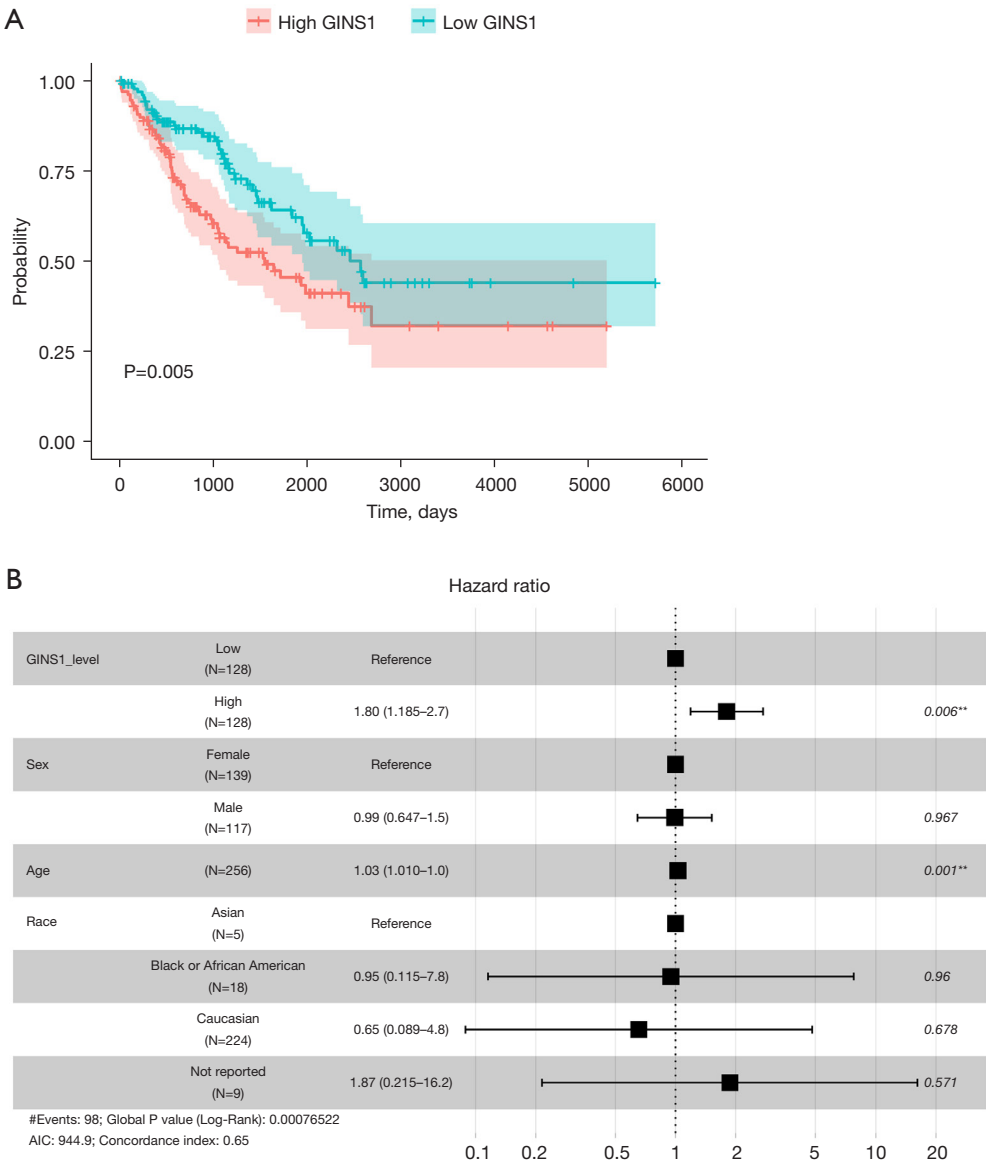

Figure 3 The sarcoma patients with high *GINS1* expression had a worse prognosis. (A) Kaplan–Meier survival analysis of high-*GINS1* and low-*GINS1* sarcoma patients in TCGA. (B) Multivariate Cox regression analysis of sarcoma patients in TCGA. A HR >1 indicates a higher death risk, whereas HR <1 indicates a lower death risk. **, P<0.01. TCGA, The Cancer Genome Atlas; HR, hazard ratio.

natural killer (NK) cells, and T follicular helper cells infiltration, yet negatively associated with M2 macrophages, gamma delta T cells, and CD8 T cells infiltration (*Figure 5B*). In addition, we revealed that M0 and M2 macrophages infiltrated significantly differently between sarcoma patients with high and low *GINS1* expression, respectively (*Figure 5C*).

Prediction of miRNAs targeting GINS1 in sarcoma

To predict the miRNAs negatively regulating *GINS1* in sarcoma, we first observed 31 remarkably downregulated miRNAs in the sarcoma cell lines than in the control cells in the GSE69470 dataset (*Figure 6A,6B*). Subsequently, we used the miRDB database to obtain 87 miRNAs

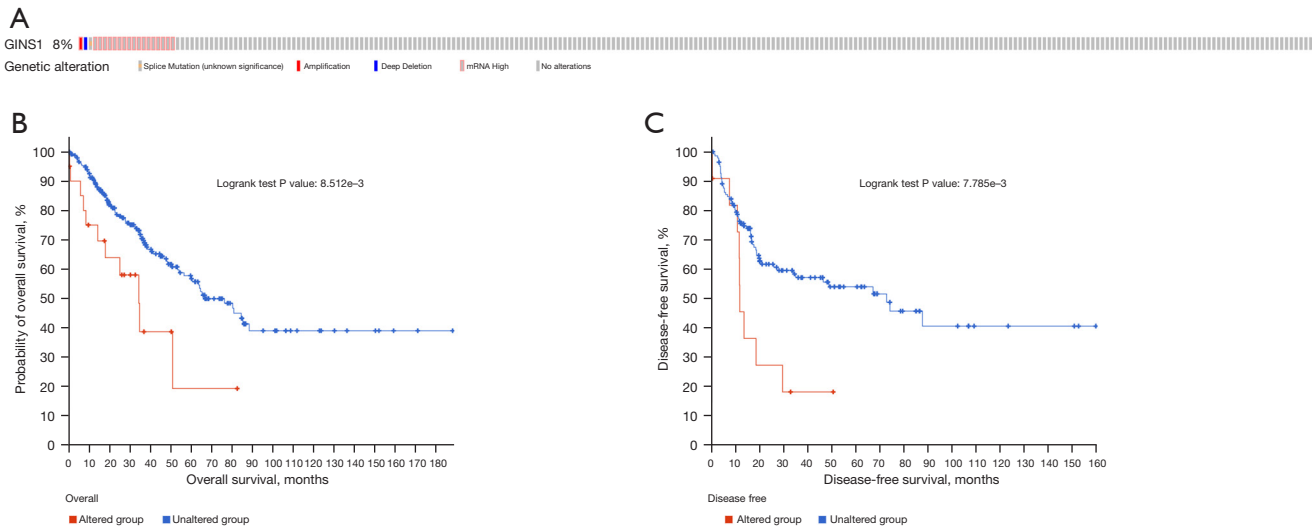

Figure 4 Analysis of genetic alteration of *GINS1* in sarcoma patients. (A) OncoPrint visual summary of variation on the query of *GINS1*. (B,C) *GINS1* genetic alteration associated with poor OS and DFS of sarcoma. OS, overall survival; DFS, disease-free survival.

targeting *GINS1* (*Table 2*). The Venn diagram displayed one overlapping miRNA, namely hsa-miR-376a-3p, which may regulate *GINS1* in sarcoma (*Figure 6C*).

Discussion

The GINS complex, first discovered in eukaryotic cells by Takayama *et al.*, is crucial for DNA replication cell cycle regulation, and participates in cell multiplication and apoptosis (24-26). Among the GINS complex, *GINS1* plays an important role in the prognosis of patients with synovial sarcoma, which inspired our interest in the impact of *GINS1* on all sarcoma types. Here, we explored the relationship between *GINS1* and sarcoma patient prognosis and attempted to identify the regulatory mechanism of *GINS1* in sarcoma using various bioinformatic tools. Our study collectively demonstrated that the expression of *GINS1* is high in sarcomas and is related to poor prognosis.

There have been numerous studies on GINS complex in various tumors. In lung cancer, *GINS1*, *GINS3*, and *GINS4* have been highly expressed and associated with a poor prognosis (27-29). Additionally, colorectal cancer patients with *GINS3* overexpression show a poorer prognosis in contrast to those with low expression (30). Studies have also demonstrated that silencing *GINS2* or *GINS3* arrests the colon cancer cell cycle (31,32). Besides, *GINS4* is overexpressed in gastric cancer and is vital for facilitating gastric cancer cell proliferation and growth via *Rac1* and *CDC42* (33). The aforesaid evidence suggests that the GINS complex plays an essential role in tumor development. We initially investigated the expression profile of *GINS1* and its association with patient prognosis in sarcomas. Higher *GINS1* expression was observed in sarcomas than in the control group, and *GINS1* expression in metastatic sarcomas was significantly higher than that in the non-metastatic group. Moreover, in TCGA database, higher *GINS1* expression in sarcoma was related to a poor prognosis, suggesting that high *GINS1* expression might be correlated with carcinogenesis and progression of sarcoma.

Subsequently, we studied the genetic alteration of *GINS1* in sarcomas. *GINS1* was altered in 8% of the studied sarcoma specimens, and the elevated mRNA expressions were the highest number of alterations. *GINS1* alteration was remarkably associated with worse OS and DFS in sarcoma, indicating that *GINS1* may play a critical role in sarcoma prognosis.

Over the past decade, tumor immunotherapy has made noticeable progress in clinical practice and is emerging as a highly effective treatment option in a variety of tumors (34,35). Previous studies have identified that tumor-infiltrating immunocytes, an essential component of the tumor microenvironment, play pivotal roles in tumor progression (36-38). Nevertheless, the efficacy of immunotherapy in sarcomas is restricted due to the

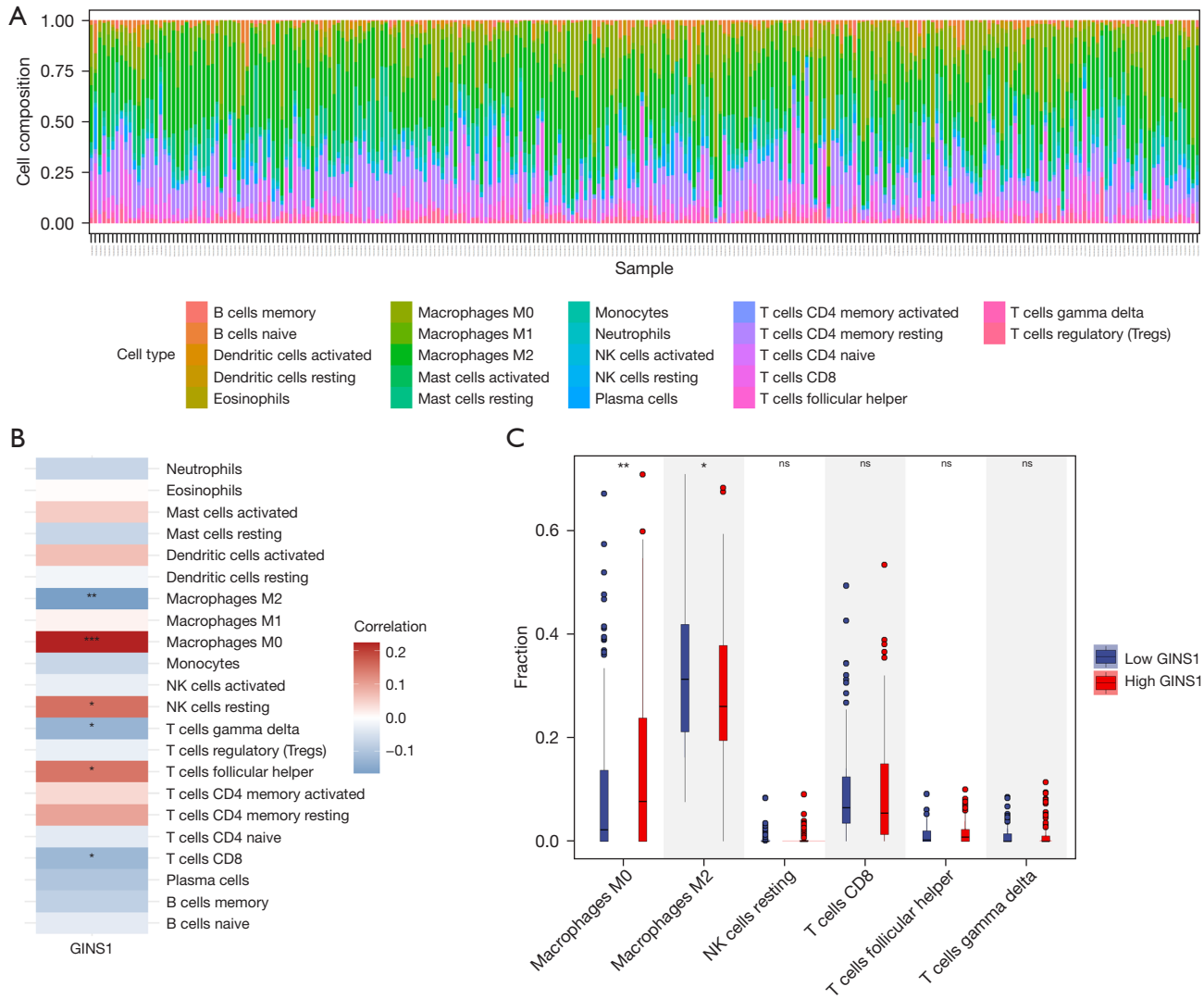

Figure 5 Immunocyte infiltration in sarcomas with differentially expressed *GINS1*. (A) The infiltration of 22 immunocytes in 256 sarcoma patients. (B) Correlation between differentially expressed *GINS1* and immunocyte infiltration. (C) Differential infiltration of immunocytes between high-*GINS1* expression and low-*GINS1* expression samples. *, P<0.05; **, P<0.01; ***, P<0.001; ns, no significant.

heterogeneity of these tumors (39). As shown in *Figure 5*, M0 and M2 macrophages' infiltration were dramatically different between the high and low *GINS1* expression sarcomas. Additionally, *GINS1* was closely associated with the infiltration of M0 and M2 macrophages. Macrophages play a dominant role in the immune microenvironment of sarcomas (40), indicating that *GINS1* is implicated in the tumor immune microenvironment and might affect sarcoma prognosis by influencing immune cell infiltration, which requires further validation. Furthermore, to explore the upstream regulatory mechanism of *GINS1* in sarcoma, we predicted the potential miRNAs which might regulate *GINS1* using the GSE69470 dataset and miRDB database. Our results showed that hsa-miR-376a-3p might regulate *GINS1* expression, which may affect the progression of sarcomas.

Our study has a few limitations. Another independent patient cohort is required to validate the prognostic value

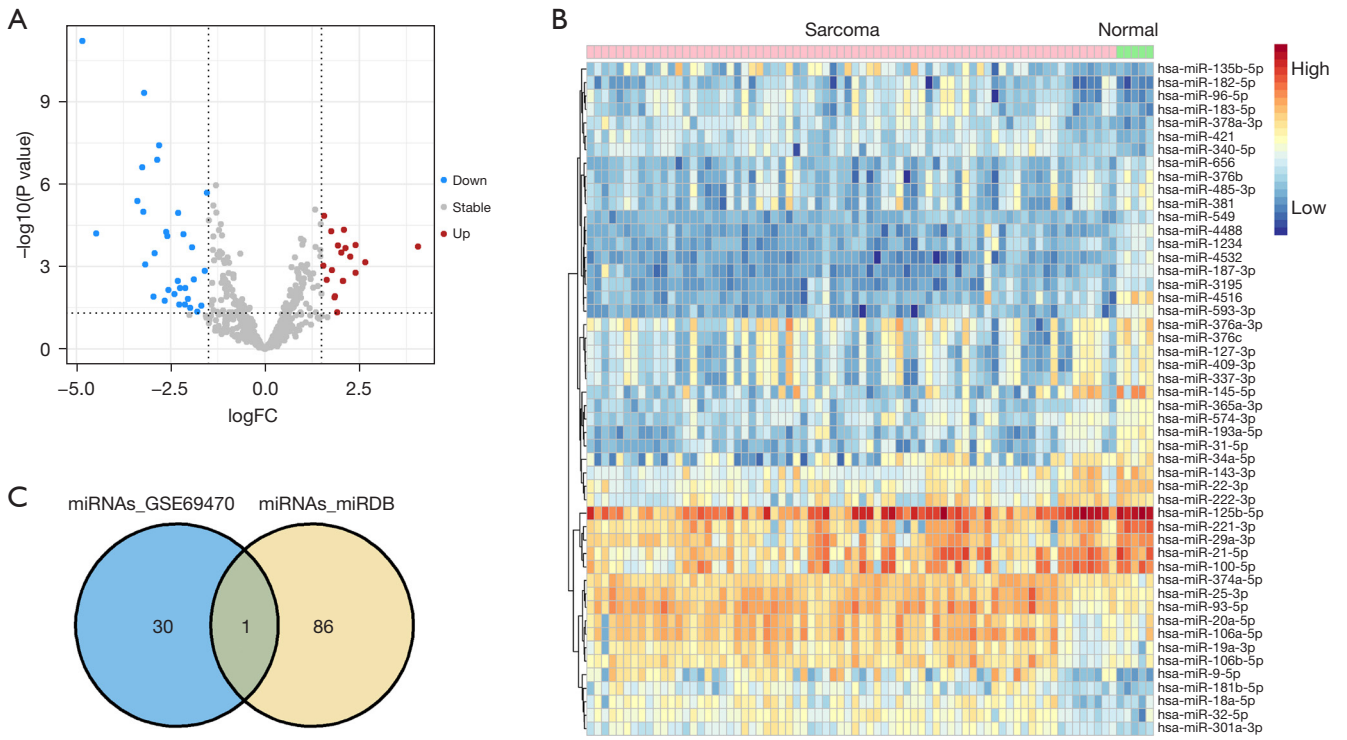

Figure 6 Prediction of miRNAs targeting *GINS1* in sarcoma. (A) Volcano of the DEMs between sarcoma cell lines and the control cells (GSE69470). (B) Heatmap of the DEMs. (C) One overlapping miRNA in the Venn diagram. miRNA, microRNA; DEM, differentially expressed miRNA; FC, fold change.

Table 2 The miRNAs targeting *GINS1* in miRDB database

mRNA	miRNAs targeting mRNA
GINS1	hsa-miR-519a-2-5p, hsa-miR-520b-5p, hsa-miR-1323, hsa-miR-548o-3p, hsa-miR-4306, hsa-miR-767-5p, hsa-miR-216a-5p, hsa-miR-4477a, hsa-miR-126-5p, hsa-miR-16-2-3p, hsa-miR-195-3p, hsa-miR-101-5p, hsa-miR-4482-3p, hsa-miR-1283, hsa-miR-4684-5p, hsa-miR-6880-5p, hsa-miR-7151-3p, hsa-miR-4644, hsa-miR-4643, hsa-miR-185-5p, hsa-miR-373-5p, hsa-miR-616-5p, hsa-miR-371b-5p, hsa-miR-4328, hsa-miR-190a-3p, hsa-miR-302a-5p, hsa-miR-425-5p, hsa-miR-4662a-5p, hsa-miR-4713-5p, hsa-miR-3613-3p, hsa-miR-6512-5p, hsa-miR-6734-3p, hsa-miR-5696, hsa-miR-376b-3p, hsa-miR-376a-3p, hsa-miR-4478, hsa-miR-3177-5p, hsa-miR-1289, hsa-miR-6780a-5p, hsa-miR-1295b-3p, hsa-miR-12123, hsa-miR-4480, hsa-miR-186-3p, hsa-miR-9718, hsa-miR-4433a-3p, hsa-miR-628-5p, hsa-miR-150-5p, hsa-miR-3120-3p, hsa-miR-7106-5p, hsa-miR-6820-3p, hsa-miR-3164, hsa-miR-4518, hsa-miR-651-3p, hsa-miR-7515, hsa-miR-6799-5p, hsa-miR-19b-3p, hsa-miR-486-5p, hsa-miR-7977, hsa-miR-3689b-3p, hsa-miR-6779-5p, hsa-miR-3689c, hsa-miR-3689a-3p, hsa-let-7c-3p, hsa-miR-1273h-5p, hsa-miR-30b-3p, hsa-miR-3929, hsa-miR-6127, hsa-miR-5187-3p, hsa-miR-3165, hsa-miR-3682-3p, hsa-miR-8070, hsa-miR-103b, hsa-miR-6500-3p, hsa-miR-642a-3p, hsa-miR-4666b, hsa-miR-642b-3p, hsa-miR-6876-5p, hsa-miR-8063, hsa-miR-4476, hsa-miR-6756-3p, hsa-miR-3127-3p, hsa-miR-1251-5p, hsa-miR-539-5p, hsa-miR-6811-3p, hsa-miR-551b-5p, hsa-miR-6825-5p, hsa-miR-6504-3p

miRNA, microRNA.

of *GINS1* in sarcoma. Additionally, the results of our study were based only on bioinformatics analyses, and further *in vivo* and *in vitro* studies are needed to verify our findings.

Conclusions

We showed that *GINS1* is highly expressed in sarcomas and is closely associated with poor prognosis. *GINS1* is expected to be a potential prognostic biomarker and therapeutic target for sarcoma.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-524/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-524/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-524/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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